Remarks

Claims 24-35 are pending in this application. The specification is amended to correct a typographical error, as suggested by the Examiner. Claims 24, 27-29, 31, and 34-35 are amended to delete the term "about." No new matter has been added.

Applicants respectfully submit that all of the pending claims are allowable for the following reasons.

The Rejection of the Claims Under 35 U.S.C. § 103 Should Be Withdrawn

A. The Claimed Invention

The claimed invention is directed, in part, to a single unit dosage form of thalidomide comprising 50, 100, or 200 mg of thalidomide in a size 4, 2, or 0 capsule, respectively.

At the time of this invention, a thalidomide formulation in a size 0 capsule, which contains 50 mg of thalidomide was approved by FDA and commercially available in the U.S. by the applicant. This formulation contained about 350 mg of carrier, providing a formulation with 12.5 weight percent of thalidomide. Some of the patients on thalidomide therapy were required to take as much as 800 to 1000 mg of thalidomide per day, which required the intake of 16 to 20 size 0 capsules per day. This large number of capsules required for thalidomide therapy raised serious concern to the applicant and doctors with regard to the patients' comfort and compliance to the therapy. As a result, the inventors sought, among other things, a thalidomide formulation in a size 0 capsule which contains 200 mg of thalidomide, four times as much thalidomide than the commercially available formulation, without compromising the bioavailability of the existing approved and commercially available formulation.

In order to create a dosage form having a higher amount of thalidomide, but having same capsule size, the amount of carriers had to be drastically reduced. The Examiner recognizes the need to reduce the amount of excipients in the Office Action. In this particular case, the formulation needed to contain about 40-50 weight percent of thalidomide, as opposed to 12.5 weight percent in the FDA-approved commercially available formulation.

In making pharmaceutical formulations, working with limited amount of carriers poses several problems. Such is particularly true with regard to thalidomide because of its low solubility in water and poor flow characteristics; each of which presents a major problem in the creation of novel thalidomide formulations. Furthermore, because of its low solubility, bioavailability is also an issue in formulating thalidomide. Yet,

controlling the properties such as flow characteristics and bioavailability of a formulation is precisely what pharmaceutical carriers are used for. However, as they had to limit the amount of pharmaceutical carriers, the inventors did not have the flexibility of liberally using pharmaceutical carriers to control such properties.

Despite these difficulties, the inventors achieved a formulation of thalidomide that contains 200 mg of thalidomide in a size 0 capsule, as recited by claim 31. Next, this achievement gave rise to a formulation that contains 100 mg of thalidomide in a size 2 capsule, as recited by claim 29. In turn, the inventors created a formulation that contains 50 mg of thalidomide in a size 4 capsule, as recited by claim 24.

These new formulations possessed excellent flow characteristics for ease of manufacturing. In addition, these formulations were discovered to be bioequivalent (*i.e.*, showed comparable bioavailability) to the FDA-approved thalidomide formulation commercially available in the U.S. The bioavailability data (*e.g.*, dissolution test data) were previously submitted to FDA in connection with the supplemental NDA application 21-430 ("sNDA"), and are also attached hereto as **Exhibit A** for the Examiner's consideration.

B. The Claims Are Not Obvious

On pages 2-5 of the Office Action, claim 24 is rejected as allegedly obvious over U.S. Patent No. 5,643,915 to Andrulis, Jr. *et al.* ("Andrulis") and Gennaro, *Remington: The Science and Pharmacy*, pp. 1642-1649 (1995) ("Gennaro"). In particular, it is alleged that claim 24 is obvious because: 1) Andrulis discloses a tablet containing 60 mg of thalidomide and a capsule containing 80 mg of thalidomide; 2) although Andrulis does not teach the specific amount of thalidomide recited by claim 24, *i.e.*, 50 mg, it discloses a range of amount that encompasses 50 mg; 3) Gennaro teaches that capsules are preferred over tablets, and also discloses the fill weights of capsules of different sizes and various carriers; 4) 50 mg thalidomide in a size 0 capsule was available at the time of the filing; and 5) it is obvious to make smaller capsules by decreasing the amount of carrier. Applicants respectfully disagree.

Under current law, a prior art reference or references cannot render a claim obvious unless the PTO provides evidence that the reference or references meet a three-part test for *prima facie* obvious. To begin with, the prior art reference or references must provide "motivation, suggestion, or teaching of the desirability of making the specific combination that was made by the applicant." *See In re Kotzab*, 217 F.3d 1365, 1370, 55 U.S.P.Q.2d 1313, 1316 (Fed. Cir. 2000); *Princeton Biochemicals, Inc. v. Beckman Coulter, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d 1051, 1054 (Fed. Cir. 2005). Where one

reference is relied upon by the PTO, there must be a suggestion or motivation to modify the teachings of that reference. *See In re Kotzab*, 217 F.3d at 1370, 55 U.S.P.Q.2d at 1316-17. Where an obviousness determination relies on the combination of two or more references, there must be some suggestion or motivation to combine the references. *See WMS Gaming Inc. v. International Game Technology*, 184 F.3d 1339, 1355, 51 U.S.P.Q.2d 1385, 1397 (Fed. Cir. 1999); *Princeton Biochemicals, Inc.*, 2005 WL 1355127, at *4, 75 U.S.P.Q.2d at 1054; *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334, 63 U.S.P.Q.2d 1374, 1387 (Fed. Cir. 2002). Second, the prior art references cited by the PTO must suggest to one of ordinary skill in the art that the invention would have a reasonable expectation of success. *See In re Dow Chemical* , 837 F.2d 469, 473, 5 U.S.P.Q.2d 1529, 1532 (Fed. Cir. 1988); *Boehringer Ingelheim Vetmedica, Inc.*, 320 F.3d 1339, 1354, 65 U.S.P.Q.2d 1961, 1971 (Fed. Cir. 2003); *Noelle v. Lederman*, 355 F.3d 1343, 1352, 69 U.S.P.Q.2d 1508, 1516 (Fed. Cir. 2004). Further, "[b]oth the suggestion and the reasonable expectation of success 'must be founded in the prior art, not in the applicant's disclosure.'" *Noelle*, 355 F.3d at 1352, 69 U.S.P.Q.2d at 1515-16 (quoting *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1991)). Finally, the PTO must show that the prior art references, either alone or in combination, teach or suggest each and every limitation of the rejected claims. *See Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461, 1473, 43 U.S.P.Q.2d 1481, 1490 (Fed. Cir. 1997); *Litton Systems, Inc. v. Honeywell, Inc.*, 87 F.3d 1559, 1569, 39 U.S.P.Q.2d 1321, 1327 (Fed. Cir. 1996). Applicants respectfully submit that these criteria are not met by the references cited by the Examiner.

In essence, the basis of the rejection appears to be that since 50 mg thalidomide in a size 0 capsule was available, a smaller capsule containing the same amount of thalidomide could have been made by simply reducing the amount of carrier. Office Action, page 5. Presumably, Andrulis and Gennaro are cited to show that making of a specific thalidomide formulation is allegedly within the skill of the art. *Id.*, pages 3-5. Further, the Examiner also appears to contend that Gennaro, by allegedly teaching that capsules are preferred over tablets, provides a motivation to make and use capsule formulations. *Id.* at page 4. Applicants respectfully disagree with each of these contentions for the following reasons.

First, Applicants respectfully submit that the cited references fail to disclose or suggest all of the limitations of claim 24. As the Examiner recognizes, none of the cited references, or prior art thalidomide formulations for that matter, disclose a single unit dosage form in the form of a size 4 capsule comprising 50 mg of thalidomide and 74 mg of a carrier, as recited by claim 24. Furthermore, none of the cited references suggest a

formulation with the specific amounts of thalidomide and a carrier recited by claim 24, in the specific size of capsule recited by claim 24. This is because the cited references disclose nothing whatsoever regarding the desirability of a formulation that contains 50 mg of thalidomide and 74 mg of a carrier, in a size 4 capsule. For this reason alone, Applicants respectfully submit that the rejection of claim 24 should be withdrawn.

Second, Applicants respectfully submit that there would have been no reasonable expectation of successfully obtaining the formulation recited by claim 24. In this regard, the Examiner appears to suggest that the formulation recited by claim 24 could have been made from the FDA-approved commercial formulation by simply reducing the amount of carriers. Contrary to the Examiner's contention, however, the formulation recited by claim 24 could not have been made by simply reducing the amount of carrier used for known formulations. This is because, as discussed above, carriers are used to impact certain properties of pharmaceutical formulations, such as flow characteristics and bioavailability. Therefore, especially in the case of thalidomide, which has a low solubility, a formulation, which possesses manufacturing and pharmacokinetic properties similar to another formulation containing the same amount of thalidomide, but which should fill a smaller capsule size, cannot be obtained by simply reducing the amount of carriers.[1] Consequently, Applicants respectfully submit that the rejection of claim 24 should be withdrawn for this additional reason.

Third, Applicants respectfully submit that no required motivation is provided by the references cited by the Examiner. In this regard, Applicants note that the Examiner may be contending that Gennaro, by allegedly disclosing that capsules are preferable over tablets, provides motivation to modify the tablet formulation containing 60 mg of thalidomide, as disclosed in Example 6 of Andrulis, to arrive at the claimed capsule formulation. Apart from the fact that it is unclear whether the tablet formulation disclosed in Andrulis has comparable properties as the claimed capsule formulation, a tablet formulation cannot simply be encapsulated to obtain a capsule formulation with comparable properties because tablets and capsules have different properties with regard to, for example, the manufacturing characteristics, dissolution and bioavailability.

Furthermore, Applicants point out that Gennaro does not stand for the proposition that capsules are generally preferred over tablets. This is because Gennaro merely discloses that "encapsulation of medicinal agents remains a popular method for administering drugs," but does not disclose that capsules are always preferred over tablets.

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[1] If the Examiner's proposition were true, one would have simply made a formulation with the active ingredient only and fitted the formulation into an even smaller capsule size.

Gennaro, page 1642 (emphasis added). Although Gennaro discloses that capsules have some advantages over tablets, Applicants point out that the reverse is also true. This is evidenced by the fact that, as Gennaro itself discloses, "the industry prepares approximately 75% of its solid dosage forms as compressed tablets," and that "market surveys have indicated a consumer preference of ... 39.6% for tablets." *Id.* Therefore, Gennaro does not stand for the general proposition that tablets are preferred over capsules.

For at least the foregoing reasons, Applicants respectfully submit that no *prima facie* case of obviousness is established by the cited references with regard to claim 24, and thus request that the rejection of claim 24 be withdrawn. However, even assuming, for the sake of argument, that a *prima facie* case of obviousness were established with regard to claim 24, Applicants submit that claim 24 is still not obvious in view of the unexpected results. As the Examiner will see, the data show that the formulation recited by claim 24 (*i.e.*, 50 mg in size 4 capsule) is bioequivalent to the commercial thalidomide formulation previously approved by the FDA (*i.e.*, 50 mg in size 0 capsule), based on pharmacokinetic criteria such as C_{max}, AUC (0-t), and AUC (0-inf). *See* **Exhibit A**. The fact that a formulation with about 40 weight percent of thalidomide could be made to behave similarly to a formulation with about 12.5 weight percent of thalidomide is surprising considering the difficulties associated with using limited amount of carriers, as discussed above. Consequently, Applicants respectfully submit that claim 24 is not obvious over the cited references, and thus request that the rejection of claim 24 be withdrawn.

On pages 6-7 of the Office Action, claims 25-28 are rejected as allegedly obvious over Andrulis and Gennaro, further in view of U.S. Patent No. 6,914,067 to Govindarajan *et al.* ("Govindarajan"). In particular, it is alleged that these claims are obvious since Govindarajan discloses several binders and carriers, which include those recited by these claims. Office Action, page 7. Apart from the fact that the pharmaceutical composition disclosed in Govindarajan is not identical to the claimed formulation, and thus, the disclosure of Govindarajan is irrelevant to the claimed invention, Applicants respectfully point out that, regardless of what Govindarajan discloses, claims 25-28 cannot be obvious because these claims depend from claim 24. In other words, the disclosure of the excipients in Govindarajan does not overcome the deficiencies of the primary references, much less suggest the specific claimed formulation or excipients. Therefore, for at least the same reasons discussed in connection with the rejection of claim 24, Applicants respectfully request that the rejection of claims 25-28 be withdrawn.

On pages 7-8 of the Office Action, claims 29-30 are rejected as allegedly obvious over Andrulis and Gennaro, further in view of Baker *et al.*, Abstract 54,

Hematology Society of Australia and New Zealand (2000) ("Baker"), Teo *et al.*, *J. Clin. Pharmacol.*, 39: 1162-1168 (1999) ("Teo I"), and Teo *et al.*, *Biopharmaceutics & Drug Disposition*, 21: 33-40 (2000) ("Teo II"). In particular, it is alleged that since Baker, Teo I and Teo II respectively disclose Sauramide™, Tortuga™ and Talizer™, all of which are thalidomide formulations containing 100 mg of thalidomide, it would have been obvious to make and use the claimed formulation by "adjust[ing] the amount of carrier and capsule size to fit one's purposes." Office Action, page 8.

First of all, Applicants respectfully disagree with the proposition that the amount of carrier and capsule size can be easily adjusted "to fit one's purposes" for essentially the same reasons discussed in connection with the rejection of the claim 24. In addition, Applicants respectfully point out that the two Teo references cited by the Examiner attest to the fact that one cannot arbitrarily adjust the amount of carriers and expect the resulting formulation to have properties comparable to the original formulation.

Teo I discloses the comparison between the properties of Celgene's thalidomide formulation (*i.e.*, then commercially available formulation with 50 mg thalidomide in size 0 capsule) and Tortuga™, available from Cia Zeetechnica Agaria of Sao Paulo. *See* Teo I, page 1163, right column. Upon examining various pharmacokinetic properties of these two formulations, Teo I concludes that, while "Celgene formulations were bioequivalent when comparing C_{max}, t_{max}, and AUC," there was "significant variability in plasma levels from the Tortuga formulation, giving a mean profile that was distinctly different from the two Celgene formulations." *Id.*, Abstract (emphasis added). Consequently, Teo I clearly shows that two formulations containing the same active ingredient exhibit distinctive pharmacokinetic properties, and thus, demonstrates that a formulation with similar properties cannot be obtained by simply adjusting "the amount of carriers to fit one's purposes," as the Examiner suggests. Office Action, page 8.

Teo II is in complete accord. Teo II discloses a comparison between the properties of Celgene's 50 mg thalidomide formulation and Talizer™ (100 mg thalidomide), when those formulations were administered at a single oral dose of 200 mg thalidomide. *See* Teo II, Abstract and page 34. Upon examining the pharmacokinetics under fasted and non-fasted conditions, authors of Teo II observe that Talizer "resulted in a lower mean C_{max}, and slower terminal decline in plasma thalidomide concentrations compared with" Celgene formulation. Teo II, Abstract. The mean C_{max} for Celgene formulation, under both fasted and non-fasted conditions, was found to be about two times greater than Talizer™. *Id.* Further, under fasted conditions, Celgene formulation was found to have about 10% greater AUC than Talizer™. *Id.* Consequently, Teo II also shows

that two formulations containing the same active ingredients behave quite differently depending on how they are formulated.

In addition, Teo I and II, by disclosing that the pharmacokinetics of the active ingredient are affected by how the compositions are formulated, and that Celgene formulation generally has better pharmacokinetic properties than other available thalidomide formulations, actually discourage those of ordinary skill in the art from even considering a new thalidomide formulation with pharmacokinetic properties comparable to, or better than, the then-available Celgene formulation. Despite this, the inventors of this application successfully obtained new thalidomide formulations that had properties comparable to the old formulation, while using lower amount of carriers.[2] Consequently, Applicants respectfully submit that claims 29-30 are not obvious, and thus request that the rejection of these claims be withdrawn.

On pages 8-9 of the Office Action, claim 31 is rejected as allegedly obvious over Andrulis and Gennaro, further in view of Scheffler *et al.*, *Clinical Pharmacology and Therapeutics*, 65(5): 483-490 (1999) ("Scheffler"). In particular, the Examiner alleges that claim 31 is obvious based on her assertion that: 1) Andrulis allegedly "used for an example 'a gelatin capsule containing 200 mg of thalidomide'," referring to column 10, line 30-31 of Andrulis; 2) Scheffler teaches that a 200 mg/day oral dosage is well tolerated; and thus, 3) the combined reference would have motivated those of ordinary skill in the art to make single dosage form containing 200 mg thalidomide, and it would have been obvious to make a formulation with 200 mg thalidomide in a form of a size 0 capsule. Office Action, page 9. Applicants respectfully disagree.

First, Applicants respectfully disagree with the Examiner's contention that Andrulis' alleged disclosure of "a gelatin capsule containing 200 mg thalidomide" and Scheffler's disclosure that 200 mg doses are well tolerated would somehow motivate those of ordinary skill in the art to make single dosage form containing 200 mg thalidomide. This is because Andrulis' alleged disclosure of a gelatin capsule containing 200 mg thalidomide is <u>in connection with a combination therapy</u>, and is merely mentioned in a passing without any concrete examples containing that amount. In addition, Andrulis provides no disclosure or teaching of why the capsule containing specifically 200 mg thalidomide is desirable. Furthermore, Scheffler's disclosure that 200 mg thalidomide was well-tolerated does not specifically motivate those of ordinary skill in the art to make a formulation with that specific amount, because 200 mg dose could be obtained by administering four 50 mg

[2] As shown by **Exhibit A**, referred to above.

dosage forms available at the time of this invention, which is precisely what Scheffler did. *See* Scheffler, page 484, right column. Consequently, Applicants respectfully submit that no required motivation is provided by these references, contrary to the Examiner's contention.

More important, however, is the fact that, even if those of ordinary skill in the art were somehow motivated to make a dosage form containing 200 mg of thalidomide,[3] they would not have had a reasonable expectation of successfully obtaining a single unit dosage form in a size 0 capsule comprising 200 mg of thalidomide and only 297.5 mg of a carrier, as recited by claim 31, which also has pharmacokinetic and other properties comparable to the then available thalidomide formulation, for the reasons discussed in connection with the rejections of other claims. Consequently, Applicants respectfully submit that claim 31 is also not obvious, and thus, request that the rejection of claim 31 be withdrawn.

On pages 9-10 of the Office Action, claims 32-35[4] are rejected as allegedly obvious over Andrulis, Gennaro, Govindarajan, and Scheffler. Regardless of what these references disclose in connection with claims 32-35, however, as these claims depend from claim 31, Applicants respectfully point out that these claims are not obvious for the same reasons discussed with regard to claim 31. In other words, the disclosure of Govindarajan does not overcome the deficiencies of Andrulis, Gennaro and/or Scheffler, much less suggest the specific claimed formulation or excipients. Consequently, Applicants respectfully request that the rejection of claims 32-35 be also withdrawn.

Conclusion

In sum, Applicants respectfully submit that all of the pending claims are allowable because: 1) no *prima facie* case of obviousness is established by the references cited by the Examiner for any of the pending claims because a formulation, which possesses properties to another formulation containing the same amount of thalidomide, but which can fit into a smaller capsule size, cannot be made by simply reducing the amount of carriers, as alleged by the Examiner; and 2) even assuming, *arguendo*, a *prima facie* case of obviousness is established by the cited references, pending claims are still not obvious in view of the unexpected showing that the claimed formulations are bioequivalent to the previously known thalidomide formulation despite the fact that lower amounts of carriers

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[3] Applicants submit that they would not have, for the reasons discussed above.

[4] Although the Office Action indicates that claims 31-35 are rejected under this rejection, based on the reasons for rejection, Applicants believe that claims 32-35 are rejected.

are used for the claimed formulations. In view of the foregoing, Applicants respectfully request that the rejection of the pending claims be withdrawn.

No fee is believed due for the submission of this paper. If any fees are required for the submission of this paper, or to avoid abandonment of this application, please charge such fees to Jones Day Deposit Account No. 503013.

Respectfully submitted,

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